Intramolecular Cyclisation of δ -iminoacetilenes:

a new entry to pyrazino[1,2-*a*]indoles.

Giorgio Abbiati,^{*,†} Antonio Arcadi,[‡] Alessandra Belinazzi,[†] Egle Beccalli,[†] Elisabetta Rossi,[†]

Simona Zanzola.[§]

Supporting information

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Experimental: general details.

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F₂₅₄ thin-layer plates were employed for thin layer chromatography (TLC). Silica gel 40-63 micron/60A was employed for flash column chromatography. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer using KBr tablets for solids and NaCl disks for oils. Proton NMR spectra were recorded at room temperature in CDCl₃, at 200 MHz, with residual chloroform as the internal reference ($\delta_{\text{H}} = 7.27$ ppm). ¹³C NMR spectra were recorded at room temperature in CDCl₃ at 50.3 MHz, with the central peak of chloroform as the internal reference ($\delta_{\text{C}} = 77.3$ ppm). The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those due to methylene and quaternary carbons. Two-dimensional NMR experiments (NOESY) were used, where appropriate, to aid in the assignment of signals in the proton spectra. Indole-2-carbaldehyde, 2-acetyl indole and 2-benzoyl-indole were prepared according to described methods. The ammonia in methanol 2M solution was purchased from standard chemical suppliers. Microwave assisted reactions were performed in a MILESTONE microSYNT multimode labstation, using 12 mL sealed glass vessels. The reaction times specified in tables 4 and 6 in the text include the “ramp times”. The internal temperature was detected with a optical fibres sensor. “PE” refers to the fraction of petroleum ether with boiling point of 40-60 °C. “EtOAc” means ethyl acetate and “TEA” means triethylamine. Indole-2-carbaldehyde,¹ 2-acetyl-indole,² 2-benzoyl-indole³ and 1-propargyl-1*H*-indole-2-carbaldehyde **1a**⁴ were prepared according to literature.

Compounds characterization data:

1-[3-(4-Chloro-phenyl)-prop-2-ynyl]-1H-indole-2-carbaldehyde 1c: Reaction time: 1 h. Eluent for chromatography: PE/EtOAc (9:1). Yield: 259 mg, 88%. Yellow solid. Mp: 78 °C. IR: ν = 1667, 1614 cm^{-1} . ^1H NMR: δ = 5.70 (s, 2H, CH_2), 7.22-7.34 (m, 6H, arom.), 7.50 (dt, 1H, arom., 3J = 8.1, 4J = 1.1 Hz), 7.64 (d, 1H, arom., 3J = 8.1 Hz), 7.79 (d, 1H, arom. 3J = 8.1 Hz), 9.94 (s, 1H, CHO) ppm. ^{13}C NMR: δ = 34.8, 83.2, 84.8, 111.0, 118.7, 121.0, 121.6, 123.7, 126.8, 127.5, 128.7, 133.1, 134.6, 134.7, 140.3, 182.8 ppm. $\text{C}_{18}\text{H}_{12}\text{ClNO}$ (293.75): calcd. C 73.60, H 4.12, N 4.77; found C 73.51, H 4.09, N 4.80.

1-[3-(3-Trifluoromethyl-phenyl)-prop-2-ynyl]-1H-indole-2-carbaldehyde 1d: Reaction time: 1 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 288 mg, 88%. Light brown solid. Mp: 90-93 °C. IR: ν = 1671, 1613 cm^{-1} . ^1H NMR: δ = 5.72 (s, 2H, CH_2), 7.26 (dt, 1H, arom. 3J = 7.0, 4J = 1.2 Hz), 7.35 (s, 1H, C3-H arom.), 7.44 (m, 1H, arom.), 7.50-7.68 (m, 5H, arom.), 7.80 (d, 1H, arom. 3J = 8.0 Hz), 9.95 (s, 1H, CHO) ppm. ^{13}C NMR: δ = 34.7, 82.7, 85.5, 110.9, 118.8, 121.7, 123.5, 123.6, 123.7 ($^1J_{\text{C-F}}$ = 272), 125.1 ($^3J_{\text{C-F}}$ = 4), 126.8, 127.6, 128.7 ($^3J_{\text{C-F}}$ = 4), 128.8, 130.9 ($^2J_{\text{C-F}}$ = 33), 134.7, 135.0, 140.3, 182.8 ppm. ESI-MS m/z (%): 328 [M^+ + 1] (100), 130 (25). $\text{C}_{19}\text{H}_{12}\text{F}_3\text{NO}$ (327.30): calcd. C 69.72, H 3.70, N 4.28; found C 69.81, H 3.72, N 4.25.

1-[3-(4-Methoxy-phenyl)-prop-2-ynyl]-1H-indole-2-carbaldehyde 1e: Reaction time: 1 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 176 mg, 61%. Yellow solid. Mp: 72 °C. IR: ν = 1668, 1605, 1251 cm^{-1} . ^1H NMR: δ = 3.77 (s, 3H, CH_3), 5.66 (s, 2H, CH_2), 6.78 (d, 2H, arom., 3J = 8.8 Hz), 7.18-7.29 (m, 7H, arom.), 7.29 (s, 1H, C3-H arom.), 7.47 (m, 1H, arom.), 7.64 (dd, 1H, arom., 3J = 8.4, 4J = 0.8 Hz), 7.75 (dt, 1H, arom., 3J = 8.1, 4J = 0.8 Hz), 9.92 (s, 1H, CHO) ppm. ^{13}C NMR: δ = 35.0, 55.5, 82.5, 84.3, 111.4, 114.1, 114.8, 118.7, 121.6, 123.7, 126.9, 127.5, 133.1, 134.8, 140.5, 159.9, 182.9 ppm. APCI(+)-MS m/z (%): 291 [M^+ + 2] (18), 290 [M^+ + 1] (100). $\text{C}_{15}\text{H}_{15}\text{NO}_2$ (289.33): calcd. C 78.87, H 5.23, N 4.84; found C 78.95, H 5.19, N 4.81.

1-{1-[3-(4-Chloro-phenyl)-prop-2-ynyl]-1H-indol-2-yl}-ethanone 1h: Reaction time: 2 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 256 mg, 83%. Yellow solid. Mp: 107-109 °C. IR: ν =

1658, 1614, 1088 cm^{-1} . ^1H NMR: δ = 2.67 (s, 1H, CH_3), 5.72 (s, 2H, CH_2), 7.19-7.32 (m, 5H, arom.), 7.37 (s, 1H, C3-H arom.), 7.46 (dt, 1H, arom. 3J = 8.0, 4J = 1.1 Hz), 7.60 (d, 1H, arom., 3J = 8.4 Hz), 7.75 (d, 1H, arom. 3J = 8.0 Hz), ppm. ^{13}C NMR: δ = 28.0, 35.0, 82.7, 85.5, 110.9, 113.4, 121.2, 121.4, 123.2, 126.2, 126.5, 128.6, 133.1, 133.7, 134.4, 139.6, 191.6 ppm. $\text{C}_{19}\text{H}_{14}\text{ClNO}$ (307.77): calcd. C 74.15, H 4.58, N 4.55; found C 74.21, H 4.55, N 4.58.

1-{1-[3-(3-Trifluoromethyl-phenyl)-prop-2-ynyl]-1H-indol-2-yl}-ethanone 1i: Reaction time: 3 h. Eluent for chromatography: PE/EtOAc (95:5). Yield: 311 mg, 91%. Yellow solid. Mp: 67 °C. IR: ν = 1656, 1617, 1237 cm^{-1} . ^1H NMR: δ = 2.68 (s, 3H, CH_3), 5.74 (s, 2H, CH_2), 7.23 (m, 1H, arom.), 7.38 (s, 1H, C3-H arom.), 7.42-7.62 (m, 6H, arom.), 7.76 (d, 1H, arom. 3J = 7.7 Hz) ppm. ^{13}C NMR: δ = 28.1, 35.1, 82.4, 86.4, 110.9, 113.6, 121.6, 123.4, 123.8, 125.1 ($^3J_{\text{C-F}}$ = 4), 126.5, 126.6 ($^1J_{\text{C-F}}$ = 272), 126.8, 128.9 ($^3J_{\text{C-F}}$ = 4), 131.0 ($^2J_{\text{C-F}}$ = 33), 134.0, 135.1, 135.2, 139.7, 192.0 ppm. ESI-MS m/z (%): 342 [M^+ + 1] (100). $\text{C}_{20}\text{H}_{14}\text{F}_3\text{NO}$ (341.33): calcd. C 70.38, H 4.13, N 4.10; found C 70.30, H 4.11, N 4.12.

1-[1-(3-Pyrimidin-5-yl-prop-2-ynyl)-1H-indol-2-yl]-ethanone 1j: Reaction time: 3.5 h. Eluent for chromatography: PE/EtOAc (8:2). Yield: 231 mg, 84%. Light brown solid. Mp: 148 °C. IR: ν = 1665, 1611 cm^{-1} . ^1H NMR: δ = 2.68 (s, 3H, CH_3), 5.77 (s, 2H, CH_2), 7.25 (m, 1H, arom.), 7.40 (d, 1H, C3-H arom., 4J = 0.7 Hz.), 7.44-7.58 (m, 2H, arom.), 7.77 (d, 1H, arom., 3J = 8.0 Hz), 8.70 (bs, 2H, C2'-H – C6'-H pyr.), 9.10 (bs, 1H, C4'-H pyr.) ppm. ^{13}C NMR: δ = 28.1, 35.1, 77.2, 92.1, 110.8, 113.8, 119.4, 121.7, 123.5, 126.4, 126.9, 133.8, 139.6, 157.1, 159.2, 191.7 ppm. ESI-MS m/z (%): 276 [M^+ + 1] (100), 100 (26). $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}$ (275.30): calcd. C 74.17, H 4.76, N 15.26; found C 74.28, H 4.74, N 15.20.

{1-[3-(4-Chloro-phenyl)-prop-2-ynyl]-1H-indol-2-yl}-phenyl-methanone 1m: Reaction time: 2 h. Eluent for chromatography: PE/EtOAc (9:1). Yield: 307 mg, 83%. Light brown solid. Mp: 113 °C. IR: ν = 1629, 1512 cm^{-1} . ^1H NMR: δ = 5.72 (s, 2H, CH_2), 7.10 (d, 1H, C3-H arom., 4J = 0.7 Hz), 7.20-7.31 (m, 5H, arom.), 7.45-7.75 (m, 6H, arom.), 7.97 (m, 2H, arom.) ppm. ^{13}C NMR: δ = 35.1, 83.1, 85.7, 111.1, 116.4, 121.3, 121.6, 123.5, 126.5, 126.6, 128.5, 128.7, 130.0, 132.6, 133.3,

134.2, 134.6, 139.4, 140.0, 188.8 ppm. ESI-MS m/z (%): 370 [$M^+ + 1$] (100), 206 (41), 100 (42).

$C_{24}H_{16}ClNO$ (369.84): calcd. C 77.94, H 4.36, N 3.79; found C 77.81, H 4.39, N 3.78.

Phenyl-{1-[3-(3-trifluoromethyl-phenyl)-prop-2-ynyl]-1H-indol-2-yl}-methanone 1n: Reaction time: 2 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 327 mg, 81%. White solid. Mp: 93 °C. IR: $\nu = 1634, 1614, 1236\text{ cm}^{-1}$. 1H NMR: $\delta = 5.74$ (s, 2H, CH_2), 7.12 (d, 1H, C3-H arom., $^4J = 0.7$ Hz), 7.22-7.30 (m, 1H, arom.), 7.34-7.46 (m, 1H, arom.), 7.50-7.76 (m, 9H, arom.), 7.98 (d, 2H, arom., $^3J = 6.6$ Hz) ppm. ^{13}C NMR: $\delta = 35.1, 82.7, 86.3, 110.9, 116.4, 121.7, 123.5, 123.8, 124.2$ ($^1J_{C-F} = 273$), 125.1 ($^3J_{C-F} = 4$), 126.6, 126.7, 128.5, 128.8 ($^3J_{C-F} = 4$), 128.9, 129.9, 131.0 ($^2J_{C-F} = 33$), 132.6, 134.3, 135.1, 139.4, 139.9, 188.8 ppm. ESI-MS m/z (%): 404 [$M^+ + 1$] (100).

$C_{25}H_{16}F_3NO$ (403.40): calcd. C 74.43, H 4.00, N 3.47; found C 74.36, H 4.01, N 3.49.

{1-[3-(4-Methoxy-phenyl)-prop-2-ynyl]-1H-indol-2-yl}-phenyl-methanone 1o: Reaction time: 2 h. Eluent for chromatography: PE/EtOAc (98:2). Yield: 314 mg, 86%. Light brown solid. Mp: 72 °C. IR: $\nu = 1642, 1607, 1248\text{ cm}^{-1}$. 1H NMR: $\delta = 3.76$ (s, 3H, CH_3), 5.68 (s, 2H, CH_2), 6.75 (d, 2H, arom., $^3J = 9.2$ Hz), 7.05 (d, 1H, C3-H arom., $^4J = 0.7$ Hz), 7.20-7.29 (m, 4H, arom.), 7.41-7.71 (m, 5H, arom.), 7.95 (d, 2H, arom., $^3J = 6.6$ Hz) ppm. ^{13}C NMR: $\delta = 35.2, 55.5, 83.2, 84.1, 111.3, 114.0, 114.9, 116.2, 121.5, 123.3, 126.5, 128.4, 130.0, 132.5, 133.5, 134.3, 139.5, 140.0, 159.8, 188.8$ ppm. ESI-MS m/z (%): 366 [$M^+ + 1$] (100). $C_{25}H_{19}NO_2$ (365.42): calcd. C 82.17, H 5.24, N 3.83; found C 81.98, H 5.21, N 3.86.

3-Methyl-pyrazino[1,2-a]indole 2a: Eluent for chromatography: PE/EtOAc (85:15). Yellow-green solid. Mp: 173 °C. IR: $\nu = 1619, 1530\text{ cm}^{-1}$. 1H NMR: $\delta = 2.52$ (s, 3H, CH_3), 6.97 (s, 1H, C10-H arom.), 7.42 (m, 2H, arom.), 7.91 (m, 2H, arom.), 8.00 (s, 1H, C4-H arom.), 9.00 (d, 1H, C1-H arom. $^4J = 1.4$ Hz) ppm. ^{13}C NMR: $\delta = 20.9, 94.7, 110.8, 113.4, 122.0, 122.3, 123.5, 128.5, 129.0, 129.4, 132.4, 146.5$ ppm. $C_{12}H_{10}N_2$ (182.22): calcd. C 79.10, H 5.53, N 15.37; found C 79.06, H 5.55, N 15.39.

3-[1-(4-Chloro-phenyl)-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'c: Eluent for chromatography: PE/EtOAc (97:3). Yellow solid. Mp: 151 °C. IR: $\nu = 1620, 1562, 1086\text{ cm}^{-1}$. 1H

NMR: δ = 4.93 (d, 2H, CH₂, 4J = 1.5 Hz), 6.28 (s, 1H, =C-H), 6.86 (s, 1H, C10-H arom.), 7.14-7.25 (m, 1H, arom.), 7.35 (m, 4H, arom.), 7.72 (d, 1H, arom. 3J = 8.0 Hz), 7.86 (d, 2H, arom. 3J = 8.4 Hz), 8.36 (s, 1H, C1-H arom.) ppm. ^{13}C NMR: δ = 44.4, 105.6, 109.5, 121.3, 123.2, 124.5, 125.4, 128.3, 128.6, 128.8, 132.0, 133.5, 134.5, 138.0, 138.4, 149.3 ppm. C₁₈H₁₃ClN₂ (292.76): calcd. C 73.85, H 4.48, N 9.57; found C 73.98, H 4.45, N 9.58.

3-(4-Chloro-benzyl)-pyrazino[1,2-a]indole 2c: Eluent for chromatography: PE/EtOAc (97:3).

Orange solid. Mp: 124 °C. IR: ν = 1616, 1091 cm⁻¹. ^1H NMR: δ = 4.11 (s, 2H, CH₂), 7.03 (s, 1H, C10-H arom.), 7.32-7.50 (m, 5H, arom.), 7.85-7.92 (m, 3H, arom.), 7.94 (s, 1H, C4-H arom.), 9.02 (d, 1H, C1-H arom., 4J = 1.5 Hz) ppm. ^{13}C NMR: δ = 40.4, 95.9, 111.1, 114.7, 122.6, 122.7, 124.0, 128.8, 129.0, 129.4, 129.6, 130.7, 132.7, 135.1, 137.7, 147.1 ppm. C₁₈H₁₃ClN₂ (292.76): calcd. C 73.85, H 4.48, N 9.57; found C 73.88, H 4.50, N 9.60.

3-[1-(3-Trifluoromethyl-phenyl)-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'd:

Eluent for chromatography: PE/EtOAc (98:2). Yellow oil. IR: ν = 1614, 1567 cm⁻¹. ^1H NMR: δ = 4.94 (d, 2H, CH₂, 4J = 1.5 Hz), 6.32 (t, 1H, =C-H, 4J = 1.5 Hz), 6.87 (s, 1H, C10-H arom.), 7.16-7.57 (m, 5H, arom.), 7.73 (dt, 1H, arom., 3J = 8.1, 4J = 1.1 Hz), 8.09 (m, 1H, arom.), 8.22 (s, 1H, arom. C2'-H), 8.37 (s, 1H, C1-H arom.) ppm. ^{13}C NMR: δ = 44.3, 105.8, 109.5, 121.4, 123.2, 124.1, 124.2 ($^3J_{\text{C-F}}$ = 4), 124.6 ($^1J_{\text{C-F}}$ = 270), 125.5, 127.5 ($^3J_{\text{C-F}}$ = 4), 128.3, 128.7, 128.8, 130.8 ($^2J_{\text{C-F}}$ = 33), 133.9, 136.8, 138.1, 139.5, 149.9 ppm. C₁₉H₁₃F₃N₂ (326.32): calcd. C 69.93, H 4.02, N 8.58; found C 70.00, H 4.05, N 8.61.

3-(3-Trifluoromethyl-benzyl)-pyrazino[1,2-a]indole 2d: Eluent for chromatography: PE/EtOAc (98:2). Yellow solid. Mp: 114 °C. IR: ν = 1614, 1535 cm⁻¹. ^1H NMR: δ = 4.17 (s, 2H, CH₂), 7.00 (s, 1H, C10-H arom.), 7.41-7.58 (m, 5H, arom.), 7.63 (s, 1H, C4-H arom.), 7.88-7.94 (m, 2H, arom.), 8.00 (s, 1H, C2'-H arom.), 9.02 (d, 1H, C1-H arom., 4J = 1.8 Hz) ppm. ^{13}C NMR: δ = 41.0, 95.6, 111.0, 114.7, 125.5, 122.6, 123.7 ($^3J_{\text{C-F}}$ = 4), 123.9, 124.4 ($^1J_{\text{C-F}}$ = 272), 126.0 ($^3J_{\text{C-F}}$ = 4), 128.8, 129.3, 129.5, 129.6, 131.2 ($^2J_{\text{C-F}}$ = 32), 132.7, 134.9, 140.5, 147.4 ppm. C₁₉H₁₃F₃N₂ (326.32): calcd. C 69.93, H 4.02, N 8.58; found C 69.86, H 3.99, N 8.59.

3-[1-(4-Methoxy-phenyl)-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'e: Eluent for chromatography: PE/EtOAc (98:2). Yellow solid. Mp: 140 °C. IR: ν = 1637, 1569, 1249 cm^{-1} . ^1H NMR: δ = 3.83(s, 3H, CH_3), 4.90 (s, 2H, CH_2), 6.26 (s, 1H, =C-H), 6.79 (s, 1H, C10-H arom.), 6.91 (d, 2H, arom., 3J = 8.8 Hz), 7.17 (m, 1H, arom.), 7.33 (m, 2H, arom.), 7.68 (d, 1H, arom. 3J = 8.1 Hz), 7.85 (d, 2H, arom. 3J = 8.8 Hz), 8.30 (s, 1H, C1-H arom.) ppm. ^{13}C NMR: δ = 44.5, 55.5, 104.8, 109.4, 114.0, 121.1, 123.0, 125.0, 125.5, 123.2, 127.8, 129.0, 135.9, 137.9, 148.3, 159.2 ppm (one signal obscured). ESI-MS m/z (%): 289 [$\text{M}^+ + 1$] (100). $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ (288.34): calcd. C 79.14, H 5.59, N 9.72; found C 79.25, H 5.61, N 9.68.

3-(4-Methoxy-benzyl)-pyrazino[1,2-a]indole 2e: Eluent for chromatography: PE/EtOAc (96:4). Yellow solid. Mp: 105 °C. IR: ν = 1611, 1584, 1251 cm^{-1} . ^1H NMR: δ = 3.81 (s, 1H, CH_3), 4.06 (s, 2H, CH_2), 6.89 (d, 2H, arom., 3J = 8.4 Hz), 6.95 (s, 1H, C10-H arom.), 7.22 (m, 3H, arom.), 7.39 (m, 2H, arom.), 7.86 (m, 3H, arom.), 9.00 (s, 1H, C1-H arom.) ppm. ^{13}C NMR: δ = 40.4, 55.5, 95.1, 111.0, 114.3, 122.3, 122.5, 123.7, 128.7, 129.4, 129.7, 130.3, 131.3, 136.5, 147.0, 158.6 ppm (one signal obscured). ESI-MS m/z (%): 289 [$\text{M}^+ + 1$] (100), 181 (18). $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ (288.34): calcd. C 79.14, H 5.59, N 9.72; found C 79.20, H 5.58, N 9.70.

1,3-Dimethyl-pyrazino[1,2-a]indole 2f: Eluent for chromatography: PE/EtOAc (8:2). Yellow solid. Mp: 82 °C. IR: ν = 1622 cm^{-1} . ^1H NMR: δ = 2.49 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 6.94 (s, 1H, C10-H arom.), 7.39 (m, 2H, arom.), 7.88 (m, 3H, arom.), ppm. ^{13}C NMR: δ = 21.0, 22.2, 94.2, 111.0, 111.7, 121.9, 122.2, 123.3, 128.3, 129.3, 129.5, 131.9, 154.4 ppm. $\text{C}_{13}\text{H}_{12}\text{N}_2$ (196.25): calcd. C 79.56, H 6.16, N 14.27; found C 79.50, H 6.12, N 14.25.

3-[1-(4-Chloro-phenyl)-meth-(Z)-ylidene]-1-methyl-3,4-dihydro-pyrazino[1,2-a]indole 2'h: Eluent for chromatography: PE/EtOAc (98:2). Yellow-orange solid. Mp: 132 °C. IR: ν = 1549, 1521, 1089, cm^{-1} . ^1H NMR: δ = 2.61 (s, 3H, CH_3), 4.85 (d, 2H, CH_2 , 4J = 1.6 Hz), 6.16 (t, 1H, =C-H, 4J = 1.6 Hz), 6.89 (s, 1H, C10-H arom.), 7.14-7.38 (m, 5H, arom.), 7.76 (d, 1H, arom. 3J = 8.1 Hz), 7.90 (m, 2H, arom.) ppm. ^{13}C NMR: δ = 22.6, 44.2, 103.9, 109.6, 121.1, 122.2, 122.9, 124.9,

127.9, 128.6, 129.3, 131.9, 133.1, 134.9, 137.6, 138.5, 157.2 ppm. C₁₉H₁₅ClN₂ (306.79): calcd. C 74.38, H 4.93, N 9.13; found C 74.32, H 4.94, N 9.16.

3-(4-Chloro-benzyl)-1-methyl-pyrazino[1,2-a]indole 2h: Eluent for chromatography: PE/EtOAc (98:2). Pale yellow solid. Mp: 144 °C. IR: ν = 1491, 1456, 1092 cm⁻¹. ¹H NMR: δ = 2.77 (s, 3H, CH₃), 4.08 (s, 2H, CH₂), 6.96 (s, 1H, C10-H arom.), 7.28-7.41 (m, 6H, arom.), 7.76 (s, 1H, C4-H arom.), 7.80-7.91 (m, 2H, arom.) ppm. ¹³C NMR: δ = 22.3, 40.5, 94.6, 111.0, 112.8, 122.1, 122.2, 123.5, 128.4, 128.8, 129.4, 129.8, 130.6, 132.4, 135.0, 137.8, 154.9 ppm. ESI-MS m/z (%): 306 [M⁺ +1] (100). C₁₉H₁₅ClN₂ (306.79): calcd. C 74.38, H 4.93, N 9.13; found C 74.36, H 4.90, N 9.18.

1-Methyl-3-[1-(3-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'i: Eluent for chromatography: PE/EtOAc (98:2). Yellow oil. IR: ν = 1614, 1560 cm⁻¹. ¹H NMR: δ = 2.63 (s, 3H, CH₃), 4.90 (d, 2H, CH₂, ⁴*J* = 1.8 Hz), 6.25 (t, 1H, =C-H, ⁴*J* = 1.8 Hz), 6.93 (s, 1H, C10-H arom.), 7.19-7.48 (m, 5H, arom.), 7.72 (d, 1H, arom., ³*J* = 8.1 Hz), 8.10 (m, 1H, arom.), 8.32 (s, 1H, arom. C2'-H) ppm. ¹³C NMR: δ = 22.6, 44.1, 104.2, 109.6, 121.1, 121.8, 123.0, 123.8 (³*J*_{C-F} = 4), 125.1, 126.5 (¹*J*_{C-F} = 272), 127.4 (³*J*_{C-F} = 4), 127.9, 128.7, 129.2, 130.7 (²*J*_{C-F} = 33), 133.6, 137.0, 137.7, 139.6, 157.9 ppm. C₂₀H₁₅F₃N₂ (340.34): calcd. C 70.58, H 4.44, N 8.23; found C 70.64, H 4.42, N 8.28.

1-Methyl-3-(3-trifluoromethyl-benzyl)-pyrazino[1,2-a]indole 2i: Eluent for chromatography: PE/EtOAc (98:2). Yellow solid. Mp: 103 °C. IR: ν = 1616, 1520 cm⁻¹. ¹H NMR: δ = 2.78 (s, 3H, CH₃), 4.17 (s, 2H, CH₂), 6.97 (s, 1H, C10-H arom.), 7.37-7.56 (m, 5H, arom.), 7.65 (s, 1H, C4-H arom.), 7.82 (s, 1H, C2'-H arom.), 7.89 (m, 2H, arom.) ppm. ¹³C NMR: δ = 22.3, 41.1, 94.8, 111.0, 113.0, 122.3, 122.4, 123.6 (³*J*_{C-F} = 4), 123.7, 124.5 (¹*J*_{C-F} = 272), 126.1 (³*J*_{C-F} = 4), 128.7, 129.2, 129.5, 130.0, 131.1 (²*J*_{C-F} = 32), 132.7, 134.6, 140.7, 155.2 ppm. C₂₀H₁₅F₃N₂ (340.34): calcd. C 70.58, H 4.44, N 8.23; found C 70.56, H 4.45, N 8.29.

1-Methyl-3-[1-pyrimidin-5-yl-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'j: Eluent for chromatography: PE/EtOAc (7:3). Yellow amorphous solid. Mp: 120 (dec.) °C. IR: ν = 1560, 1407 cm⁻¹. ¹H NMR: δ = 2.60 (s, 3H, CH₃), 4.91 (d, 2H, CH₂, ⁴*J* = 1.5 Hz), 6.07 (s, 1H, =C-H), 6.93

(s, 1H, C10-H arom.), 7.18 (2, 1H, arom.), 7.35 (m, 2H, arom.), 7.70 (d, 1H, arom. $^3J = 8.1$ Hz), 9.04 (s, 1H, C4'-H pyr.), 9.25 (s, 2H, C2'-H/C6'-H pyr.) ppm. ^{13}C NMR: $\delta = 22.6, 44.1, 104.9, 109.6, 115.9, 121.4, 123.1, 125.4, 127.9, 128.7, 130.3, 132.8, 136.9, 157.1, 157.6, 158.9$ ppm.

$\text{C}_{17}\text{H}_{14}\text{N}_4$ (274.32): calcd. C 74.43, H 5.14, N 20.42; found C 74.59, H 5.19, N 20.31.

1-Methyl-3-pyrimidin-5-ylmethyl-pyrazino[1,2-a]indole 2j: Eluent for chromatography:

PE/EtOAc (7:3). Light brown solid. Mp: 156-157 °C. IR: $\nu = 1618, 1559, 1454, 1405\text{ cm}^{-1}$. ^1H NMR: $\delta = 2.76$ (s, 1H, CH_3), 4.08 (s, 2H, CH_2), 6.99 (d, 2H, arom., $^3J = 8.4$ Hz), 7.37-7.48 (m, 2H, arom.), 7.82-7.93 (m, 2H, arom.), 7.94 (s, 1H, C4-H arom.), 8.81 (bs, 2H, C2'-H/C6'-H pyr.), 9.20 (s, 1H, C4'-H pyr.) ppm. ^{13}C NMR: $\delta = 22.3, 36.0, 95.3, 111.0, 113.0, 122.5, 122.6, 123.8, 128.7, 130.0, 132.9, 133.0, 155.6, 157.4$, ppm (two signals obscured). EI-MS m/z (%): 274 [M^+] (100), 273 (90). $\text{C}_{17}\text{H}_{14}\text{N}_4$ (274.32): calcd. C 74.43, H 5.14, N 20.42; found C 74.50, H 5.16, N 20.41.

3-Methyl-1-phenyl-pyrazino[1,2-a]indole 2k: Eluent for chromatography: PE/EtOAc (99:1).

Orange oil. IR: $\nu = 1616, 1515, 1474, 1442\text{ cm}^{-1}$. ^1H NMR: $\delta = 2.59$ (s, 3H, CH_3), 7.13 (s, 1H, C10-H arom.), 7.38-7.44 (m, 2H, arom.), 7.56 (m, 3H, arom.), 7.83-7.91 (m, 2H, arom.), 8.00-8.07 (m, 3H, arom.) ppm. ^{13}C NMR: $\delta = 21.3, 96.2, 111.0, 112.3, 122.1, 122.4, 123.7, 128.4, 128.7, 128.8, 129.6, 130.0, 132.9, 138.7, 154.8$ ppm (one signal obscured). APCI(+)-MS m/z (%): 259 [$\text{M}^+ + 1$] (100), 273 (90). $\text{C}_{18}\text{H}_{14}\text{N}_2$ (258.32): calcd. C 83.69, H 5.46, N 10.84; found C 83.75, H 5.42, N 10.86.

3-[1-(4-Chloro-phenyl)-meth-(Z)-ylidene]-1-phenyl-3,4-dihydro-pyrazino[1,2-a]indole 2'm:

Eluent for chromatography: PE/EtOAc (98:2). Yellow-orange solid. Mp: 145 °C. IR: $\nu = 1549, 1529, 1088\text{ cm}^{-1}$. ^1H NMR: $\delta = 4.95$ (d, 2H, CH_2 , $^4J = 1.5$ Hz), 6.27 (s, 1H, =C-H), 6.87 (s, 1H, C10-H arom.), 7.13-7.32 (m, 1H, arom.), 7.36 (m, 4H, arom.), 7.55 (m, 3H, arom.), 7.69 (d, 1H, arom., $^3J = 8.1$ Hz), 7.95 (d, 2H, arom., $^3J = 8.4$ Hz), 8.03 (m, 2H, arom.), ppm. ^{13}C NMR: $\delta = 44.1, 106.9, 109.4, 121.2, 123.1, 123.3, 125.1, 127.8, 128.0, 128.6, 128.7, 129.3, 130.7, 132.0, 133.2, 135.0, 137.7, 137.8, 138.7, 157.5$ ppm. $\text{C}_{24}\text{H}_{17}\text{ClN}_2$ (368.86): calcd. C 78.15, H 4.65, N 7.59; found C 78.21, H 4.68, N 7.62.

3-(4-Chloro-benzyl)-1-phenyl-pyrazino[1,2-a]indole 2m: Eluent for chromatography: PE/EtOAc (98:2). Yellow solid. ^1H NMR: δ = 4.16 (s, 2H, CH_2), 6.85 (s, 1H, C10-H arom.), 7.11-7.20 (m, 2H, arom.), 7.31-7.58 (m, 8H, arom.), 7.84-8.06 (m, 5H, arom.) ppm. ESI-MS m/z (%): 369 [$\text{M}^+ + 1$] (100). (This compound was obtained in a too low amount to perform pf, IR, ^{13}C NMR and elemental analysis).

1-Phenyl-3-[1-(3-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-3,4-dihydro-pyrazino[1,2-a]indole 2'n: Eluent for chromatography: PE/EtOAc/TEA (95:2.5:2.5). Yellow solid. Mp: 102 °C (dec.). IR: ν = 1634, 1532, 1156 cm^{-1} . ^1H NMR: δ = 4.98 (d, 2H, CH_2 , 4J = 1.5 Hz), 6.35 (s, 1H, =C-H), 6.92 (s, 1H, C10-H arom.), 7.18 (m, 1H, arom.), 7.30-7.60 (m, 7H, arom.), 7.70 (d, 1H, arom. 4J = 7.7 Hz), 7.96 (m, 1H, arom.), 8.08 (m, 2H, arom.), 8.61 (s, 1H, arom. C2'-H) ppm. ^{13}C NMR: δ = 44.0, 107.2, 109.4, 121.2, 122.7, 123.2, 123.8 ($^3J_{\text{C-F}}$ = 4), 124.7 ($^1J_{\text{C-F}}$ = 272), 125.3, 127.7 ($^3J_{\text{C-F}}$ = 4), 127.8, 127.9, 128.7, 129.4, 130.7 ($^2J_{\text{C-F}}$ = 33), 130.9, 133.6, 137.1, 137.6, 137.7, 139.8, 158.1 ppm (one signal obscured). $\text{C}_{25}\text{H}_{17}\text{F}_3\text{N}_2$ (402.41): calcd. C 74.62, H 4.26, N 6.96; found C 74.64, H 4.25, N 6.94.

3-[1-(4-Methoxy-phenyl)-meth-(Z)-ylidene]-1-phenyl-3,4-dihydro-pyrazino[1,2-a]indole 2'o: Eluent for chromatography: PE/EtOAc (99:1). Orange solid. Mp: 140 °C. IR: ν = 1527, 1255 cm^{-1} . ^1H NMR: δ = 3.85 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 6.29 (s, 1H, =C-H), 6.85 (s, 1H, C10-H arom.), 6.94 (d, 2H, arom., 3J = 8.8 Hz), 7.15 (m, 1H, arom.), 7.40 (m, 2H, arom.), 7.54 (m, 3H, arom.), 7.68 (d, 1H, arom. 3J = 8.1 Hz), 7.99 (d, 2H, arom. 3J = 8.8 Hz), 8.04 (m, 2H, arom.) ppm. ^{13}C NMR: δ = 44.1, 55.5, 106.2, 109.4, 114.0, 121.0, 122.9, 124.5, 124.8, 127.8, 128.2, 128.7, 129.3, 129.4, 130.3, 132.3, 136.2, 137.5, 138.1, 156.4, 159.2 ppm. ESI-MS m/z (%): 365 [$\text{M}^+ + 1$] (100). $\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}$ (364.44): calcd. C 82.39, H 5.53, N 7.69; found C 82.55, H 5.49, N 7.68.

Computational Methods:

The structures of compounds **2a**, **2'a**, **2f**, **2'f**, **2k**, **2'k**, **2b**, **2'b**, **2g**, **2'g**, **2l** and **2'l** were subjected to a preliminary conformational analysis at semiempirical level. Semiempirical calculations were done with the Hyperchem^{®5} (6.03 release). Energy minimizations were done with semiempirical SCF calculation method AM1,⁶ using the Polak-Ribiere algorithm. The minima were re-optimised at ab-initio level (HF/6-31+G*) and the energies were finally calculated at DFT level (B3LYP/6-311+G**). Ab-initio and DFT calculations were performed with Gaussian03[®] using default options.⁷ The hybrid functional B3LYP was chosen as it generally performs well on organic molecules and the split valence 6-311+G** basis set was employed as a good compromise between speed and accuracy.⁸ The character of optimised geometries was confirmed by the absence of imaginary frequencies. All calculations were carried out assuming isolated molecules in the gas phase.

NMR kinetic study details:

In two sealed tubes, two identical samples (**A** and **B**) were prepared dissolving **1h** (154 mg, 0.5 mmol) in 2N ammonia in methanol (5 mL). Three equivalents of TiCl₄ (285 mg, 1.5 mmol) were slowly added to sample **B** (caution!). Both samples were stirred in an oil bath at 100 °C for several hours. At pre-established slot, the tubes were rapidly cooled at room temperature under running water and quotes of each sample (0.45 mL) were poured in HCl 0.1N (2 mL) and extracted twice with EtOAc (2 × 1 mL). The organic layers, dried over sodium sulfate, were evaporated to dryness and the resulting crudes were analysed by ¹H-NMR. The changing in ratio among starting product **1h**, dihydro derivative **2'h** and pyrazino derivative **2h** in function of reaction time was determined by comparing the integrals of characteristic methylene signals of **1h** (δ = 5.72 ppm), **2'h** (δ = 4.85 ppm) and **2h** (δ = 4.08 ppm). The following tables reported the calculated data:

Sample A (uncatalysed reaction of 2c)				Sample B (TiCl ₄ catalysed reaction of 2c)			
t (h)	2c (%)	5'c (%)	5c (%)	t (h)	2c (%)	5'c (%)	5c (%)
0	100	0	0	0	100	0	0
1	100	0	0	0,25	55,11	44,88	0
2	100	0	0	0,75	19,1	79,6	0
4	100	0	0	1,5	2,9	91,79	5,22
6	95,6	4,4	0	2,25	0	91,91	8,08
11	88	12	0	3,25	0	85,21	14,78
19	75,19	19,89	4,18	4,25	0	76,31	23,68
25	70,31	21,87	7,81	7,25	0	47,7	52,3
32	64,16	26,66	9,16	10	0	24,39	75,61
39	62,78	26,9	10,31	13	0	22,23	77,77
46	61,23	27,65	11,12	15	0	21,88	78,12
63	59,64	26,75	13,59				
80	57,41	26,79	15,79				
104	40	28,33	31,66				
128	35,07	24,62	40,29				
159	33,33	25,49	41,17				
183	29,67	20,87	49,45				
207	26,92	21,15	51,92				

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